Tamoxifen and beyond : antiestrogens and aromatase inhibitors in the hormonal therapy of breast cancer

Summary

In this Thesis, the results of studies on hormonal therapy of breast cancer, performed at the Medical Oncology Department of the National Cancer Institute in Genova and at the Medical Oncology Unit of the S.Croce Hospital in Cuneo, Italy, were presented. Most of the studies were performed within the framework of the cooperative group GONO (Gruppo Oncologico Nord Ovest), and some have been completed at the South West Wales Cancer Institute in Swansea, UK.

Chapter 1 provides an introduction to the studies and an overview of the questions and problems that have been addressed in the Thesis. These include monitoring and treatment of tamoxifen's estrogenic and antiestrogenic side effects, and the role of aromatase inhibitors in early and advanced breast cancer, as alternatives to tamoxifen or used in a sequential strategy.

Chapter 2 presents the results of a study aimed at assessing the role of pelvic ultrasound to screen for endometrial abnormalities associated with the use of adjuvant tamoxifen. One hundred and sixty four asymptomatic patients (110 on treatment with tamoxifen, 20 mg/day, and 54 controls) were included in the study: in the postmenopausal group, tamoxifen-treated patients had significantly thicker endometria and significantly larger uterine volume than controls. Fifty-four percent of patients on tamoxifen had an endometrial thickness $\geq$ 5 mm, often with an irregular pattern suggesting the presence of cysts. Ultrasound findings, however, did not correlate with endometrial abnormalities at biopsy. In view of its low specificity and poor positive predictive value, which is probably due to sub-epithelial changes and benign polyps induced by tamoxifen, we concluded that routine ultrasound screening in asymptomatic subjects is not recommended.

Attempts to improve on the specificity of ultrasound screening in patients on tamoxifen have included research on refinements such as the instillation of saline solution into the uterine cavity at the time of transvaginal ultrasound scanning, a technique known as sonohysterography. In **Chapter 3**, sonohysterography was used in asymptomatic postmenopausal patients on tamoxifen, who exhibited an endometrial thickness of $\geq$8 mm at transvaginal ultrasound. Forty-one patients entered the study: sonohysterography allowed to identify a normal endometrial cavity in 9 patients (21.9%), who could thus be spared a biopsy. In the remaining patients, benign polyps (n = 15, 36.6%) and endometrial atrophy (n = 14, 34.1%) were the most common findings; 3 patients (7.3%) had simple hyperplasia. Despite a modest improvement over standard transvaginal ultrasound, the proportion of false positive results remained high and we concluded that there is insufficient evidence to recommend this technique routinely in asymptomatic patients on tamoxifen.

Before the advent of aromatase inhibitors, alternative SERMs (selective estrogen receptor modulators) such as toremifene have been explored as possible alternatives to tamoxifen. In **Chapter 4**, the results of a crossover study from tamoxifen to toremifene are presented. Twenty postmenopausal breast cancer patients receiving adjuvant tamoxifen, 20 mg/day, were switched to toremifene 60 mg/day and the effects on the uterus were assessed prospectively by transvaginal ultrasound. Toremifene did not however modify previous uterine changes induced by tamoxifen. Subsequent studies by others have confirmed that both drugs cause similar ultrasound changes and vaginal

symptoms, and phase III trials in the adjuvant setting found that the incidence of endometrial cancer was not different between the two drugs.

Chapter 5 investigates treatments for one of tamoxifen's side effects associated with its antiestrogen action, i.e. menopausal symptoms. The study compared six weeks of low-dose oral megestrol acetate (MA) with three injections (on day 1, 14 and 28) of intramuscular medroxyprogesterone acetate (MPA) for the control of hot flushes in 71 postmenopausal patients with early breast cancer, of whom 73% were on adjuvant tamoxifen. Six weeks after randomization, a significant reduction (more than 50% compared to baseline) of the severity and frequency of hot flushes was observed in 67% and 75% of the patients randomized to MA and MPA, respectively. Patients treated with medroxyprogesterone acetate had a more prolonged duration of the benefit compared to megestrol, with 89% of responders still maintaining the effect at week 24, vs. 45% in the megestrol group. Today, non-hormonal treatments for hot flushes are usually preferred in breast cancer survivors, based on efficacy data from recent randomized trials: these include the antidepressants venlafaxine, fluoxetine and paroxetine, and the antiepilectic gabapentin. Our study however still provides useful clinical information for patients who do not respond to, or do not tolerate, these agents.

A series of large multicenter trials is currently exploring the role of third-generation aromatase inhibitors in the adjuvant setting, either as an alternative to tamoxifen or in a sequential fashion after tamoxifen. **Chapter 6** is a report of the early results of one of such studies, the Intergroup Exemestane Study (IES), an international, phase III, intergroup, randomized, double-blind study which recruited 4742 postmenopausal women with breast cancer who remained disease-free after 2-3 years of adjuvant tamoxifen. Participating patients were randomized to receive either exemestane 25mg/day or tamoxifen for the remainder of the 5-year period. After a median follow up of 30.6 months, 449 first events (local or metastatic recurrence, contralateral breast cancer, or death) were reported, with an hazard ratio in favor of the exemestane group of 0.68 corresponding to an absolute benefit in terms of disease-free survival of 4.7 percent. The results of this study suggest that five years of postoperative tamoxifen may be suboptimal for postmenopausal patients with estrogen-receptor positive breast cancer, adding strenght to the recommendation that AIs should be used in these patients instead or after tamoxifen.
In view of their lack of estrogenic activity, one of the potential advantages of AIs over tamoxifen is a reduction of endometrial toxicity. This is being formally assessed in a sub study within the IES trial, the preliminary results of which are presented in **Chapter 7.** Two hundred and nineteen patients randomized in the main trial participated to the sub study, and were prospectively monitored with transvaginal ultrasound. Switching to exemestane resulted in a significantly lower proportion of patients with abnormal endometrial thickness two years after randomization (41.7% with exemestane vs. 64.6% with tamoxifen. The mean endometrial thickness and the mean uterine volume were also significantly reduced. The positive changes associated with exemestane were already apparent after 6 months from randomisation.

The last chapters present applications of AIs in the setting of metastatic breast cancer. **Chapter 8** is a study of maintenance therapy with letrozole in postmenopausal patients

who responded or stabilized after first-line chemotherapy for advanced breast cancer. Fifty-eight patients were recruited and received letrozole, 2.5 mg/day starting within 8 weeks since the last cycle of chemotherapy. The median time to progression from starting letrozole was 18.5 months. Response status improved during letrozole in 15.5% of patients who had obtained less than a complete response to chemotherapy. A shorter time to progression was found in patients with abnormal CA 15-3 levels at the start of maintenance letrozole, or with levels increasing ≥25% from baseline during the first six months of letrozole therapy. Maintenance treatment was well tolerated and had no significant impact on quality of life scores. This observation is encouraging, and would warrant further confirmation in a controlled trial.

Chapter 9 is a study of sequential use of exemestane and non-steroidal AIs in advanced breast cancer. Forty patients received exemestane 25 mg daily as first anti-aromatase agent, with a clinical benefit (CB) rate (complete response + partial response + stabilization of disease for ≥24 weeks) of 67.5% and a median time to progression (TTP) of 9.6 months. In 18 patients, letrozole or anastrozole were used after failure of exemestane: the CB rate was 55.6% with a median TTP of 9.3 months. In 23 patients, exemestane was used after failure of letrozole or anastrozole: the CB rate was 43.5% with a median TTP of 5.1 months.
The study was based on previously reported observations of partial non-cross resistance between steroidal and non-steroidal Ais, but is the first to also examine the sequence of exemestane first, then letrozole or anastrozole. Clinical benefit was observed with both sequences, suggesting that the partial lack of cross-resistance between steroidal and non-steroidal AIs is independent of the sequence used.

As reviewed in **Chapter 10**, the clinical implications of the sequencing studies are that anti-aromatase drugs of the two types could be used at different times to prolong disease control, before changing to other, less tolerable treatments (such as progestins or chemotherapy). The traditional sequence of hormone therapy is also likely to change further based on the results of recent and ongoing adjuvant trials which may result in an increased number of patients exposed to AIs in the adjuvant setting, and on the introduction of new agents such as the estrogen receptor down-regulator fulvestrant.